PARP INHIBITOR AND NO-DONOR DUAL PRODRUGS AS ANTICANCER AGENTS

SUMMARY

The National Cancer Institute's Chemical Biology Laboratory seeks partners interested in collaborative research to co-develop PARP inhibitor and NO-donor hybrid prodrugs for the treatment of cancer.

REFERENCE NUMBER

E-220-2011

PRODUCT TYPE

- Therapeutics

KEYWORDS

- Therapeutic
- cancer
- nitric oxide
- poly-ADP-ribose polymerase
- PARP
- prodrug

COLLABORATION OPPORTUNITY

This invention is available for licensing.

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DESCRIPTION OF TECHNOLOGY

Poly-ADP ribose polymerase-1 (PARP-1) is a critical enzyme involved in DNA repair. The inhibition of PARP has emerged as a promising strategy in cancer therapy. Numerous PARP inhibitors have been developed and advanced into clinical trials, both for use as single agents in specific patient populations and as combination therapies with various chemotherapeutics. The induction of strand break damage to DNA, as has been demonstrated in cancer cells treated with O2-arylated diazeniumdiolates, coupled with inhibition of DNA repair by PARP inhibitors, represents a novel rationale for effective combination therapy.

Scientists at NCI's Chemical Biology Laboratory have developed prodrugs that combine structural features of the known PARP inhibitor olaparib with an O2-arylated diazeniumdiolate in one hybrid

molecule. The two-component prodrug has the advantage of delivering both a DNA damaging agent (NO) and an inhibitor of DNA repair (PARP inhibitor) simultaneously to a cancer cell. The prodrugs are activated by glutathione (GSH) and the reaction accelerated by glutathione S-transferase P1 (GSTP1), an enzyme frequently overexpressed in cancer. This mechanism consumes GSH while releasing cytotoxic NO and a PARP inhibitor simultaneously in the target cancer cell. As high levels of GSH/GSTP1 are often a feature of cancer cells, the compound is predicted to have strong synergy with other anticancer therapeutics. When compared to the PARP inhibitor olaparib, these hybrid molecules exceeded the *in vivo* anticancer potency in xenograft models, resulting in more extensive DNA strand break damage, and ultimately greater apoptosis induction, as observed *in vitro*. These compounds are predicted to have strong radio- and chemosensitizing effects.

POTENTIAL COMMERCIAL APPLICATIONS

Stand-alone cancer therapeutics or as part of a combination therapy with other cancer therapies

COMPETITIVE ADVANTAGES

Combination of a DNA damaging agent and a DNA repair inhibitor in one molecule eliminates the need to administer two separate treatments; Activation mechanism that involves overexpressed in cancers GSTP1 targets drugs to cancer cell

INVENTOR(S)

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DEVELOPMENT STAGE

- Pre-clinical (in vivo)

PATENT STATUS

- **Foreign Filed:** PCT Application No. PCT/US2012/060785 filed October 18 2012

THERAPEUTIC AREA

- Cancer/Neoplasm